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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
GUY SERRE, ET AL.	: EXAMINER: HADDAD
SERIAL NO: 10/019,439	:
FILED: MAY 8, 2002	: GROUP ART UNIT: 1644
FOR: FIBRIN CITRULLINE DERIVATIVES AND THEIR USE FOR DIAGNOSING OR TREATING RHEUMATOID ARTHRITIS	:

DECLARATION UNDER 37 C.F.R. §1. 132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:
I, Guy SERRE, state that:

1. My Curriculum vitae is attached as Annex A

2. I am a coauthor of several publications and a co-inventor of several US and granted patents in the field of rheumatoid arthritis (RA) diagnosis by antifilaggrin autoantibodies (AFAs). My main publications and US patent applications and granted patents relative to this field, are listed in Annex A.

3. I supervised experiments to obtain fibrin fragments recognized by AFAs.

4. The experiments were conducted in the following manner.

EXPERIMENTAL PROCEDURES

AFA-positive sera:

AFA-positive sera were obtained from 90 patients suffering from RA. The presence of AFAs in the sera was checked by indirect immunofluorescence on cryosections of rat oesophagus epithelium (VINCENT et al., Ann. Rheum. Dis., 48, 712-722 1989), and by

immunotransfer on human epidermal filaggrin (VINCENT et al., J. Rheumatol., 25, 838-846 1998).

In order to take in account the heterogeneity of the reactivity of the AFA-positive sera with respect to citrullinated epitopes, the 90 sera were tested against 5 different citrullinated peptides representative of major epitopes of human filaggrin recognized by the AFAs. These peptides are as follows:

E12D	ESSRDGSXHPRSHD
T12E	TGSSTGGXQGSHHE
E12H	EQSADSSXHSGSGH
cfc6	SHQESTXGXSRGRSGRSGS
cf48-65-4	TIHAHPGSXXGGRHGYHH

(X indicates a citrullyl residue)

Peptides E12D, T12E, and E12H have been described by Girbal-Neuhauser, et al. (J Immunol, 162, 585-94, 1999); peptides cfc6 and cf48-65-4 have been described by Schellekens, et al. (J Clin Invest, 101, 273-81, 1998).

The analysis was carried out by ELISA according to the protocol described by Girbal-Neuhauser, et al. (1999)

This analysis allowed us to identify 12 profiles of reactivity to the 5 peptides among the 90 sera.

These profiles are summarized in Table I.

Table I

Profile	E12D	E12H	T12E	cfc6	cf48-65-4
1	+	+	+		+
2	+	+	+		
3	+	+		+	
4	+	+			
5	+				
6	+				+
7		+			
8		+	+		+
9			+		
10				+	+
11				+	
12					+

So as to be most representative possible of the various profiles of reactivity of the AFAs, 2 mixtures, hereafter called mixtures: "A" and "B" were prepared. Each of them consists of equal parts of 10 sera representing various profiles of reactivity.

The composition of these two mixtures is indicated in Table II.

Table II

Serum	Profile	Mix
97.0459	1	A
97.0388	3	
97.1436	4	
97.0169	6	
97.0530	7	
97.0311	8	
97.0506	9	
97.0468	10	
97.0796	11	
97.0907	12	
97.1715	1	B
97.0524	1	
97.0323	2	
97.0794	4	
95.0256	5	
97.1795	5	
97.1474	9	
97.0244	10	
97.1548	11	
97.1210	12	

Control sera:

A mixture of 10 AFA-negative sera, i.e sera that do not comprise AFAs detectable either by immunofluorescence on rat oesophagus epithelium, or by immunotransfert on human epidermal filaggrin acidic variant, was used as a control.

Fibrin-derived citrullinated peptides:

The peptides tested were obtained from the sequence of the α chain and from the sequence of the β chain of fibrin [corresponding respectively to residues 36-629 and 45-491 of the chains A(a) (reference NP Accession: NP_068657) and B(ß) (reference SWISSPROT FIBB_HUMAN Prim. Accession: P02675) of fibrinogen]. Sequences of residues 1 to 629 and 1 to 491 of the A(α) and B(ß) chains of fibrinogen are respectively represented in Figures 1 A and B. The sequences in bold characters on Figure 1 are those of fibrinopeptides A and B (which were not used for the design of the citrullinated peptides).

Each chain (α or β) of fibrin was segmented in sequences of 15 contiguous amino acids, and all peptides including at least one arginyl residue were selected. In the case of peptides wherein the arginyl residue was located at the NH2- or COOH-end, a second series of peptides of 15 amino acids overlapping with the first one, was selected in order to centre the arginyl residue in the sequence. In total, 71 peptides were designed: 40 were derived from the α-chain of fibrin and 31 were derived from its β-chain. For each peptide, 2 forms were synthesized using the method of MERRIFIELD (purity = 60%): a form with arginyl residues (native form) and a form where all the arginyl residues were substituted by citrullyl residues (citrullinated form).

The list of the selected citrullinated peptides is given in Table III.

Table III

A. First series			
Chain a			
α36-50Cit $_{38,42}$	α171-185Cit $_{178,181}$	α351-365Cit $_{353}$	α456-470Cit $_{458,459}$
α66-80Cit $_{69}$	α186-200Cit $_{186,190}$	α366-380Cit $_{367}$	α501-515Cit $_{510,512}$
α81-95Cit $_{84}$	α216-230Cit $_{216,218}$	α381-395Cit $_{394}$	α546-560Cit $_{547}$
α111-125Cit $_{114,123}$	α246-260Cit $_{258}$	α396-410Cit $_{404}$	α561-575Cit $_{573}$
α126-140Cit $_{129,135,137}$	α261-275Cit $_{263,271}$	α411-425Cit $_{425}$	α591-605Cit $_{591}$
α141-155Cit $_{143}$	α276-290Cit $_{287}$	α426-440Cit $_{426}$	α621-629Cit $_{621,627}$
α156-170Cit $_{160,168}$	α306-320Cit $_{308}$	α441-455Cit $_{443}$	
Chain ß:			
β45-59Cit $_{47,53}$	β195-209Cit $_{196,199,206}$	β330-344Cit $_{334}$	β435-449Cit $_{436,445}$
β60-74Cit $_{60,72,74}$	β210-224Cit $_{224}$	β375-389Cit $_{376}$	β465-479Cit $_{478}$
β75-89Cit $_{87}$	β240-254Cit $_{246}$	β390-404Cit $_{395}$	β480-49Cit $_{485}$
β120-134Cit $_{121,124}$	β255-269Cit $_{267}$	β405-419Cit $_{410}$	
β150-164Cit $_{158}$	β285-299Cit $_{285,294}$	β420-434Cit $_{421}$	
B Second series:			
Chain a:			
α138-152Cit $_{143}$	α300-314Cit $_{308}$	α438-452Cit $_{443}$	α615-629Cit $_{621-627}$
α183-197Cit $_{186,190}$	α347-36Çit $_{353}$	α455-469Cit $_{458,459}$	
α213-227Cit $_{216,218}$	α363-377Cit $_{367}$	α542-556Cit $_{547}$	
α259-273Cit $_{263,271}$	α420-434Cit $_{425,426}$	α588-602Cit $_{591}$	
Chain ß:			
β50-64Cit $_{53,60}$	β202-216Cit $_{206}$	β281-295Cit $_{285,294}$	β474-488Cit $_{478,485}$
β116-130Cit $_{121,124}$	β215-229Cit $_{224}$	β373-387Cit $_{376}$	
β188-202Cit $_{196,199}$	β219-233Cit $_{224}$	β416-430Cit $_{421}$	
β193-207Cit $_{196,199,206}$	β236-250Cit $_{246}$	β433-447Cit $_{436,445}$	

The nomenclature used is as follows: name of the polypeptide chain (α or β) of fibrinogen from which the sequence derives, followed by: position in said chain of the amino-terminal residue of the peptide - position of the carboxy-terminal residue of the peptide. These positions are numbered starting from the N-terminal end of fibrinogen. The "Cit" mention followed by the numbers in index indicates the position of the citrullyl residues.
ELISA assay:

Each pair of peptides (citrullinated and non-citrullinated) was tested by ELISA with the 2 mixtures of sera A and B, and with the mixture of control sera.
Peptides were coated on irradiated polystyrene plates (Nunc Maxisorp). Three different buffers (acetate pH 5.0, PBS pH 7.4 and carbonate pH 9.0), were used for coating so as to optimize the chances of fixation of all the peptides (10 µg/ml) which present very heterogeneous isoelectric points (from 4 to 12 for the non-citrullinated forms). Each pair of peptides (native and citrullinated form) was tested on the same plate and a pair of control peptides (cfc6 and its native correspondent cf0 (Schellekens GA, 1998, above mentioned) —

was included for each experimentation, in order to calculate a coefficient of inter-tests variation and to carry out corrections.

After saturation with PBS-BSA 2%, the plates were incubated with the mixtures A or B or with the mixture of control sera, diluted to 1/50 in PBS 2M NaCl – BSA 2%. The reaction was revealed with peroxidase-conjugated goat's IgG directed against human IgG, diluted to 1/1000 in PBS BSA 2%. All incubations were carried out for 1 hour at 4°C and were followed by washings in PBS-Tween 0.1%.

The peroxidase activity was revealed by a solution of ortho-phenylenediamine (2mg/ml — Sigma) in hydrogen peroxide (0.03% — Sigma). The reaction was stopped after 5 minutes by 4M sulphuric acid and the optical density (OD) at 492 nm was measured with an automatic spectrophotometer (Multiskan, Thermo Labsystems).

Results:

The specific reactivity of the mixtures of sera with regard to citrullinated peptides was calculated as the difference (delta OD) between the OD obtained with the citrullinated peptide and the OD obtained with the corresponding native peptide. The results represent an average of 2 determinations. Any citrullinated peptide allowing to obtain a delta OD higher than 0,250 for at least one of the two mixtures A and B, after coating in at least one of the three buffers, was regarded as reactive.

Among the 71 citrullinated peptides analyzed, 12 peptides derived from the sequence of the a chain and 5 peptides derived from the sequence of the ß chain of fibrin were recognized by at least one of the mixtures A or B. Among these peptides, 5 peptides were very reactive (Delta OD=1.5), 8 peptides were fairly reactive (0.5=delta OD<1.5) and 4 peptides were little reactive (0.25=delta OD<0.5). Other citrullinated peptides were considered as not reactive (0=delta OD<0.25).

No reactivity with the mixture of control sera was observed. This shows that the reactive peptides are carriers of epitopes recognized by the AFAs.

The results obtained for the 17 reactive peptides are presented in Table IV.

Table IV

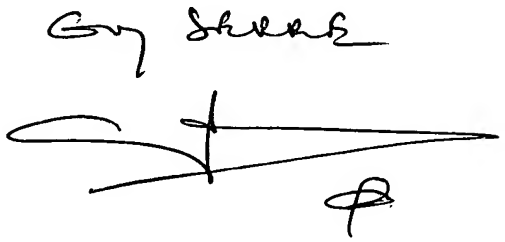
Peptide	Serum Mix	Coating buffer		
		Acetate	PBS	Carbonate
α36-50Cit $_{38,42}$	Mix A	3,998	2,687	3,432
	Mix B	4,272	2,652	2,640
α171-185Cit $_{178,181}$	Mix A	0,149	0,287	0,749
	Mix B	0,076	0,213	0,467
α246-260Cit $_{258}$	Mix A	0,044	0,000	0,000
	Mix B	0,265	0,250	0,333
α366-380Cit $_{367}$	Mix A	0,283	0,372	0,259
	Mix B	0,000	0,035	0,084
α396-410Cit $_{404}$	Mix A	0,043	0,022	0,428
	Mix B	0,153	0,167	0,201
α411-425Cit $_{425}$	Mix A	0,085	0,158	0,563
	Mix B	0,377	0,661	0,429
α501-515Cit $_{510,512}$	Mix A	0,159	0,919	0,145
	Mix B	0,723	2,598	0,792
α546-560Cit $_{547}$	Mix A	0,376	0,738	0,334
	Mix B	0,046	0,147	0,155
α561-575Cit $_{573}$	Mix A	0,050	0,298	0,012
	Mix B	0,137	0,522	0,165
α183-197Cit $_{186,190}$	Mix A	0,412	1,678	1,360
	Mix B	0,013	0,149	0,067
α259-273Cit $_{263,271}$	Mix A	0,137	0,595	0,122
	Mix B	0,208	0,690	0,196
α588-602Cit $_{591}$	Mix A	0,046	0,163	0,363
	Mix B	0,055	0,332	0,672
β60-74Cit $_{60,72,74}$	Mix A	1,015	2,064	1,270
	Mix B	2,833	2,687	2,723
β210-224Cit $_{224}$	Mix A	0,253	0,294	1,141
	Mix B	0,001	0,602	1,561
β420-434Cit $_{421}$	Mix A	0,414	0,578	0,672
	Mix B	0,003	0,000	0,028
β281-295Cit $_{285,294}$	Mix A	0,121	0,603	0,612
	Mix B	0,109	0,753	0,708
β433-447Cit $_{436,445}$	Mix A	0,355	0,482	0,436
	Mix B	0,000	0,000	0,000

5. These results are important because they demonstrate that identifying fibrin fragments that react with arthritis-specific anti-filaggrin autoantibodies can be accomplished with routine experimentation involving preparing citrullinated peptides on the basis of known sequences of fibrinogen as described in the above-identified application and testing their reactivity against AFA-positive sera using known immunoassays such as those described in the Examples of the above-identified application. More particularly, the data demonstrate that several peptides recognized by AFAs, representative of the purified citrullinated polypeptide claimed in this application, can be identified from both chains α and β of fibrin by a simple screening with AFA-positive sera.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date : January 5th, 2005

Guy SERRE



A.

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MFSMRIVCLV LSVVGTAWTA DSGEGDFLAE GGGVRGPRVV ERHQSACKDS DWPFCSDEDW 60
NYKCPSGCRM KGLIDEVNQD FTNRINKLKN SLFEYQKNNK DSHSLTTNIM EILRGDFSSA 120
NNRDNTYNRV SEDLRSRIEV LKRKVIEKVQ HIQLLQKNVR AQLVDMKRLE VDIDIKIRSC 180
RGSCSRALAR EVDLKDYEDQ QKQLEQVIAK DLLPSRDRQH LPLIKMKPVP DLVPGNFKSQ 240
LQKVPPEWKA LTDMPQMRME LERPGGNEIT RGGSTSYGTG SETESPRNPS SAGSWNSGSS 300
GPGSTGNRNP GSSGTGGTAT WKPGSSGPGS TGSWNSGSSG TGSTGNQNPG SPRPGSTGTW 360
NPGSSERGSA GHWTSESSVS GSTGQWHSES GSFRPDSPGS GNARPNNPDW GTFEEVSGNV 420
SPGTRREYHT EKLVTSKGDK ELRTGKEKVT SGSTTTTRRS CSKTVTKTVI GPDGHKEVTK 480
EVVTSEDGSD CPEAMDLGTL SGIGTLDGFR HRHPDEAAFF DTASTGKTFP GFFSPMLGEF 540
VSETESRGSE SGIFTNTKES SSHHPGIAEF PSRGKSSSYS KQFTSSTSYN RGDSTFESKS 600
YKMADEAGSE ADHEGTHSTK RGHAKSRPV                                    629
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B.

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MKRMVSWSFH KLKTMKHLLL LLLCVFLVKS QGVNDNEEGF FSARGHRPLD KKREEAPSLR 60
PAPPPISGGG YRARPAKAAA TQKKVERKAP DAGGCLHADP DLGVLCPTGC QLQEALLQQE 120
RPIRNSVDEL NNNVEAVSQT SSSSFQYMYL LKDLWQKRQK QVKDNENVVN EYSSELEKHQ 180
LYIDETVNSN IATNLRVLRS ILENLRSKIQ KLESDVSAQM EYCRTPCTVS CNIPVVSGKE 240
CEEIIRKGGE TSEMYLIQPD SSVKPYRVYC DMNTENGGWT VIQNRQDGSV DFGRKWDPYK 300
QGFGNVATNT DGKNYCGLPG EYWLGNDKIS QLTRMGPTEL LIEMEDWKGD KVKAHYGGFT 360
VQNEANKYQI SVNKYRGTAG NALMDGASQL MGENRTMTIH NGMFFSTYDR DNDGWLTSDP 420
RKQCSKEDGG GWWYNRCHAA NPNGRYYWGG QYTWDMAKHG TDDGVVWMNW KGSWYSMRKM 480
SMKIRPFFPQ Q                                                       491
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FIGURE 1

Annex A
CURRICULUM VITAE

Born in RODEZ (Aveyron -12), FRANCE
November 5th 1952
French Nationality

CURRENT POSITIONS (Toulouse University and University Hospital, FRANCE)

Professor of Cell Biology, Purpan Medical School, Toulouse III University
(from 1991)

Head of the Laboratory of Cell Biology and Cytology, Purpan University Hospital, Toulouse
(from 1997)

Director of the Unit "*Epidermis Differentiation and Rheumatoid Autoimmunity*", UMR 5165 of CNRS and Toulouse III University
Federative Research Institute (IFR30)
(from 2003)

PREVIOUS POSITIONS

1979 Assistant Professor (Department of Medical Biology, Purpan School of Medicine)

1983 Hospital Assistant (Laboratory of Cytology, Purpan University Hospital)

1986 Associate Professor (Department of Cell Biology, Purpan School of Medicine)

1986 Hospital Expert [Praticien hospitalier] (Laboratory of Cell Biology and Cytology, Purpan University Hospital)

1991 Director of the Department of Biology and Pathology of the Cell (Purpan School of Medicine)

1996 Director of the INSERM CJF 96-02 : "*Epidermis Differentiation and Rheumatoid Autoimmunity*"

2002 Director of the Department *"Epidermis Differentiation and Rheumatoid Autoimmunity*", U563 INSERM - Toulouse III University

EDUCATION/TRAINING

1979 Medicine Doctor [MD], Toulouse III University, Toulouse, FRANCE

1980 Expert in Human Pathology, *idem*

1981 Human Genetics Master's degree, *idem*

1982 Cell Biology Master's degree, *idem*

1990 Philosophia Doctor [PhD] (Human Immunopathology), Lyon I University, Lyon, FRANCE

SCIENTIFIC SOCIETY MEMBERSHIP

English speaking Societies:

- International Society of Differentiation,
- European Society for Dermatological Research,
- Society for Investigative Dermatology

French speaking Societies:

- Cell Biology Society (Société de Biologie Cellulaire de France),
- Dermatological Research Society (Société francophone de Recherche Dermatologique),
- Electronic Microscopy Society (Société Française d Microscopie Electronique),
- Society of Immunology (Société Française d'Immunologie)
- Society of Rheumatology (Société Française de Rhumatologie)

Scientific publications

1: De Rycke L, Peene I, Hoffman IE, Kruithof E, Union A, Meheus L, Lebeer K, Wyns B, Vincent C, Mielants H, Boullart L, Serre G, Veys EM, De Keyser F.: Rheumatoid factor and anticitrullinated protein antibodies in rheumatoid arthritis: diagnostic value, associations with radiological progression rate, and extra-articular manifestations. Ann Rheum Dis. 2004 Dec;63(12):1587-93.

2: Vincent C, Nogueira L, Sebbag M, Chapuy-Regaud S, Arnaud M, Letourneur O, Rolland D, Fournie B, Cantagrel A, Jolivet M, Serre G.: Detection of antibodies to deiminated recombinant rat filaggrin by enzyme-linked immunosorbent assay: a highly effective test for the diagnosis of rheumatoid arthritis. Arthritis Rheum. 2002 Aug;46(8):2051-8.

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9: Masson-Bessiere C, Sebbag M, Durieux JJ, Nogueira L, Vincent C, Girbal-Neuhauser E, Durroux R, Cantagrel A, Serre G.: In the rheumatoid pannus, anti-filaggrin autoantibodies are produced by local plasma cells and constitute a higher proportion of IgG than in synovial fluid and serum. Clin Exp Immunol. 2000 Mar;119(3):544-52.

10: Forslin K, Vincent C, Serre G, Svensson B.: Antifilaggrin autoantibodies in early rheumatoid arthritis. Scand J Rheumatol. 2000;29(5):320-2.

11: Vincent C, de Keyser F, Masson-Bessiere C, Sebbag M, Veys EM, Serre G.: Anti-perinuclear factor compared with the so called "antikeratin" antibodies and antibodies to human epidermis filaggrin, in the diagnosis of arthritides. Ann Rheum Dis. 1999 Jan;58(1):42-8.

12: Girbal-Neuhauser E, Durieux JJ, Arnaud M, Dalbon P, Sebbag M, Vincent C, Simon M, Senshu T, Masson-Bessiere C, Jolivet-Reynaud C, Jolivet M, Serre G.: The epitopes targeted by the rheumatoid arthritis-associated antifilaggrin autoantibodies are posttranslationally generated on various sites of (pro)filaggrin by deimination of arginine residues. J Immunol. 1999 Jan 1;162(1):585-94.

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18: Gomes-Daudrix V, Sebbag M, Girbal E, Vincent C, Simon M, Rakotoarivony J, Abbal M, Fournie B, Serre G.: Immunoblotting detection of so-called 'antikeratin antibodies': a new assay for the diagnosis of rheumatoid arthritis. Ann Rheum Dis. 1994 Nov;53(11):735-42.

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24: Serre G, Vincent C, Fournie B, Lapeyre F, Soleilhavoup JP, Fournie A.: [Anti-stratum corneum antibody in the rat esophagus, anti-epidermal keratin and anti-epidermis autoantibodies in rheumatoid polyarthritis and other rheumatic diseases. Diagnostic value and basic aspects] Rev Rhum Mal Osteoartic. 1986 Nov;53(11):607-14.

25: Sebbag M, Chapuy-Regaud S, Auger I, Petit-Texeira E, Clavel C, Nogueira L, Vincent C, Cornelis F, Roudier J, Serre G. : [Clinical and pathophysiological significance of the autoimmune response to citrullinated proteins in rheumatoid arthritis] Joint Bone Spine. 2004 Nov; 71(6):493-502.

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Annex A

2 – US patent and published patent application

- Granted US Patent N° 5,888,833 (March 30, 1999)

- US Patent Application published on December 2nd, 2004 under n° US 20040241767A1